10/040,010

L15 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:399003 CAPLUS
DOCUMENT NUMBER: 131:179607
TITLE: Relaxation of contracted rabbit tracheal and human bronchial smooth muscle by Y-27632 through inhibition of Ca2+ sensitization
AUTHOR(S): Yoshii, Akihiro; Iizuka, Kunihiko; Dobashi, Kunio; Horie, Takeo; Harada, Takashi; Nakazawa, Tsugio; Mori, Masatomo
CORPORATE SOURCE: First Department of Internal Medicine, Faculty of Medicine, School of Medicine; and Faculty of Health Sciences, Gunma University, Gunma, 371-8511, Japan
SOURCE: American Journal of Respiratory Cell and Molecular Biology (1999), 20(6), 1190-1200
CODEN: AJRBEL; ISSN: 1044-1549
PUBLISHER: American Lung Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mechanism of Ca2+ sensitization of contraction has not been elucidated in airway smooth muscle (SM). To det. the role of a small G protein, **rhoA** p21, and its target protein, rho-assocd. coiled coil-forming protein kinase (ROCK), in receptor-coupled Ca2+ sensitization of airway SM, we studied the effect of (+)-(R)-trans-4-(1-aminoethyl)-N-(4-pyridyl)cyclohexane carboxamide dihydrochloride, monohydrate (Y-27632), a ROCK inhibitor, on isometric contractions in rabbit tracheal and human bronchial SM. Y-27632 completely reversed 1 .mu.M carbachol (CCh)-induced contraction of intact trachea with a concn. producing half-max. inhibition of effect (IC50) of 1.29 .+-. 0.2 .mu.M (n = 5). Although 4.beta.-phorbol 12,13-dibutyrate (1 .mu.M)-induced Ca2+ sensitization was relatively resistant to Y-27632 in .alpha.-toxin-permeabilized trachea, CCh (100 .mu.M) plus guanosine triphosphate (GTP) (3 .mu.M)- and guanosine 5'-O-(3'-thiotriphosphate) (10 .mu.M)-induced contractions were relaxed completely by Y-27632 with IC50 of 1.44 .+-. 0.3 (n = 6) and 1.15 .+-. 0.3 .mu.M (n = 6). Endothelin-1 (1 .mu.M) plus GTP (3 .mu.M)-developed force was also reversed by Y-27632 with IC50 of 4.10 .+-. 1.1 .mu.M (n = 6) in the .alpha.-toxin-permeabilized bronchus. Both the rabbit and human SM expressed **rhoA** p21, ROCK I, and its isoform ROCK II. Collectively, rho/ROCK-mediated Ca2+ sensitization plays a central role in the sustained phase of airway SM contraction, and selective inhibition of this pathway may become a new strategy to resolve airflow limitation in asthma.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB The mechanism of Ca2+ sensitization of contraction has not been elucidated in airway smooth muscle (SM). To det. the role of a small G protein, **rhoA** p21, and its target protein, rho-assocd. coiled coil-forming protein kinase (ROCK), in receptor-coupled Ca2+ sensitization of airway SM, we studied the effect of (+)-(R)-trans-4-(1-aminoethyl)-N-(4-pyridyl)cyclohexane carboxamide dihydrochloride, monohydrate (Y-27632), a ROCK inhibitor, on isometric contractions in rabbit tracheal and human bronchial SM. Y-27632 completely reversed 1 .mu.M carbachol (CCh)-induced contraction of intact trachea with a concn. producing half-max. inhibition of effect (IC50) of 1.29 .+-. 0.2 .mu.M (n = 5). Although 4.beta.-phorbol 12,13-dibutyrate (1 .mu.M)-induced Ca2+ sensitization was relatively resistant to Y-27632 in .alpha.-toxin-permeabilized trachea, CCh (100 .mu.M) plus guanosine triphosphate (GTP) (3 .mu.M)- and guanosine 5'-O-(3'-thiotriphosphate) (10 .mu.M)-induced contractions were relaxed completely by Y-27632 with IC50 of 1.44 .+-. 0.3 (n = 6) and 1.15 .+-. 0.3 .mu.M (n = 6). Endothelin-1 (1 .mu.M) plus GTP (3 .mu.M)-developed force was also reversed by Y-27632 with IC50 of 4.10 .+-. 1.1 .mu.M (n = 6) in the .alpha.-toxin-permeabilized bronchus. Both the rabbit and human SM expressed **rhoA** p21, ROCK I, and its isoform ROCK II. Collectively, rho/ROCK-mediated Ca2+ sensitization plays a central role in

the sustained phase of airway SM contraction, and selective inhibition of this pathway may become a new strategy to resolve airflow limitation in asthma.

IT Rho protein (G protein)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p21rhoA; expression of **rhoA** p21, ROCK I, and ROCK II in airway smooth muscle)

IT **146986-50-7**, Y 27632
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(Y 27632; relaxation of contracted rabbit tracheal and human bronchial smooth muscle by Y-27632 through inhibition of Ca2+ sensitization)

IT 9059-32-9, GTPase 51845-53-5, Rho kinase 182372-13-0, Protein p160ROCK kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(expression of **rhoA** p21, ROCK I, and ROCK II in airway smooth muscle)

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L1           43 S E3
                E MILLS THOMAS M/IN
L2            7 S E3

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L4       138649 S E1-E12

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                SET NOTICE LOGIN DISPLAY

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L7            4 S L5

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L8            1 S  WO2001022997/PN

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L10           1 S E1/RN
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L14          22 S L12 AND (RHOA OR RHOB)
L15           5 S L14 NOT PY>=2001

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L21            5 S L20

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L24           64 S (RHOA OR RHOB)(S)(SEXUAL OR SEX OR ERECTI? OR DYSFUNCTION)
L25           35 S (RHOA OR RHOB)(S)(SEXUAL OR SEX OR ERECTI? OR (SEX?(3A)DYSFUN
L26            3 S L25 NOT PY>=2001
L27         1666 S Y-27632 OR Y27632
L28           48 S L27(L)( ERECTI? OR (SEX?(3A)DYSFUNCTION) OR PENILE OR CLITORA
L29           12 S L28 NOT PY>=2002
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L34         1463 S ( ERECTI? OR (SEX?(3A)DYSFUNCTION) OR PENILE OR CLITORA)(S)(S

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L36          305 S L35 NOT PY>=2001

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L40            1 S 129830-38-2/RN
                SET NOTICE 1 DISPLAY
                SET NOTICE LOGIN DISPLAY

     FILE 'CAPLUS' ENTERED AT 14:11:35 ON 15 JAN 2004
L41            4 S L40
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            19 RHOS
         10608 RHO
                  (RHO OR RHOS)
          1657 RHOA
           443 RHOB
        419618 SEX?
        121417 DYSFUNCT?
         11539 ERECT?
            11 PENIL
             0 CLITORA
L1           30 (RHO OR RHOA OR RHOB)(L)(SEX?(4A)DYSFUNCT? OR ERECT? OR PENIL
               OR CLITORA)

=> s l1 not py>=2001
       1597048 PY>=2001
L2           0 L1 NOT PY>=2001
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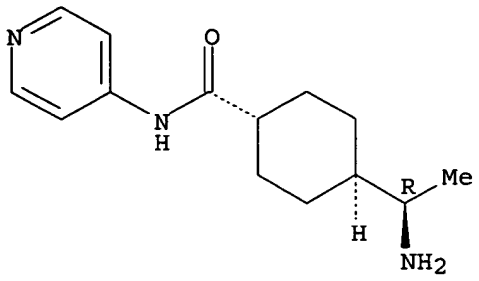
L40 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN **129830-38-2** REGISTRY
CN Cyclohexanecarboxamide, 4-[(1R)-1-aminoethyl]-N-4-pyridinyl-, dihydrochloride, trans- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cyclohexanecarboxamide, 4-(1-aminoethyl)-N-4-pyridinyl-, dihydrochloride, [4(R)-trans]-
FS STEREOSEARCH
MF C14 H21 N3 O . 2 Cl H
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL
CRN (146986-50-7)

Absolute stereochemistry. Rotation (+).



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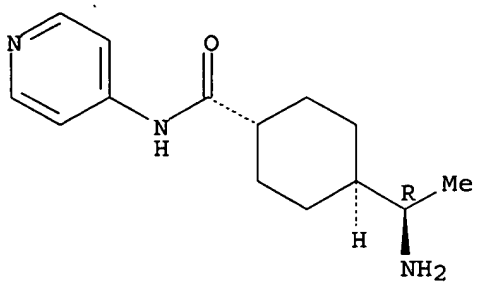
4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L12 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN **146986-50-7** REGISTRY
CN Cyclohexanecarboxamide, 4-[(1R)-1-aminoethyl]-N-4-pyridinyl-, trans- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cyclohexanecarboxamide, 4-(1-aminoethyl)-N-4-pyridinyl-, [4(R)-trans]-
OTHER NAMES:
CN Y 27632
FS STEREOSEARCH
MF C14 H21 N3 O
CI COM
SR CA
LC STN Files: BIOSIS, BIOTECHNO, CA, CAPLUS, CHEMCATS, CSCHEM, EMBASE, IMSDRUGNEWS, IMSRESEARCH, IPA, PHAR, TOXCENTER, USPAT2, USPATFULL

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

90 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
92 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L36 ANSWER 17 OF 305 MEDLINE on STN
ACCESSION NUMBER: 2001196950 MEDLINE
DOCUMENT NUMBER: 21144791 PubMed ID: 11249556
TITLE: Sildenafil.
AUTHOR: Cartledge J; Eardley I
CORPORATE SOURCE: Pyrah Department of Urology, St James University Hospital, Beckett Street, Leeds, LS9 7TF, UK..
j.cartledge@ukgateway.net
SOURCE: Expert Opin Pharmacother, (1999 Nov) 1 (1) 137-47. Ref: 58
Journal code: 100897346. ISSN: 1465-6566.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010410
Last Updated on STN: 20010410
Entered Medline: 20010405

AB Sildenafil (Viagra, Pfizer, Inc.) is a new orally effective therapy for the treatment of men with erectile dysfunction (ED). It is a specific and selective inhibitor of phosphodiesterase Type 5 (PDE5), an enzyme which is an important modulator of smooth muscle relaxation in the corpus cavernosum. In the presence of a sexual stimulus, inhibition of PDE5 results in improved **smooth muscle** relaxation within the sinusoids of the corpus cavernosum and the **penile** arteries. This results in improved erections in men with ED. In clinical trials, sildenafil has been found to be effective in improving the erections of large numbers of men with ED secondary to a range of causes. The presence of PDE5 in other tissues such as vascular smooth muscle results in side effects such as headache, flushing, indigestion and nasal congestion. These side effects are dose-dependent and well-tolerated. The introduction of sildenafil in many countries around the world has revolutionised the assessment and treatment of men with ED.

AB . . . smooth muscle relaxation in the corpus cavernosum. In the presence of a sexual stimulus, inhibition of PDE5 results in improved **smooth muscle** relaxation within the sinusoids of the corpus cavernosum and the **penile** arteries. This results in improved erections in men with ED. In clinical trials, sildenafil has been found to be effective. . .

L29 ANSWER 12 OF 12 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001036057 EMBASE

TITLE: Antagonism of Rho-kinase stimulates rat penile erection via a nitric oxide-independent pathway.

AUTHOR: Chitaley K.; Wingard C.J.; Clinton Webb R.; Branam H.; Stopper V.S.; Lewis R.W.; Mills T.M.

CORPORATE SOURCE: K. Chitaley, Department of Physiology, University of Michigan, Ann Arbor, MI 48109, United States. kanchanc@umich.edu

SOURCE: Nature Medicine, (2001) 7/1 (119-122).
Refs: 26
ISSN: 1078-8956 CODEN: NAMEFI

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Relaxation of the smooth muscle cells in the cavernosal arterioles and sinuses results in increased blood flow into the penis, raising corpus cavernosum pressure to culminate in **penile erection** (1). Nitric oxide, released from non-adrenergic/ non-cholinergic nerves, is considered the principle stimulator of cavernosal smooth muscle relaxation(2-4), however, the inhibition of vasoconstrictors (that is, norepinephrine and endothelin-1, refs. 5-9) cannot be ignored as a potential regulator of **penile erection**. The calcium-sensitizing .rho.-A/Rho-kinase pathway may play a synergistic role in cavernosal vasoconstriction to maintain **penile** flaccidity. Rho-kinase is known to inhibit myosin light chain phosphatase(10-12), and to directly phosphorylate myosin lightchain (in solution), altogether resulting in a net increase in activated myosin and the promotion of cellular contraction(10,11,13-16). Although Rho-kinase protein and mRNA have been detected in cavernosal tissue(17), the role of Rho-kinase in the regulation of cavernosal tone is unknown. Using pharmacologic antagonism (**Y-27632**, ref. 13, 18), we examined the role of Rho-kinase in cavernosal tone, based on the hypothesis that antagonism of Rho-kinase results in increased corpus cavernosum pressure, initiating the **erectile** response independently of nitric oxide. Our finding, that Rho-kinase antagonism stimulates rat **penile erection** independently of nitric oxide, introduces a potential alternate avenue for the treatment of **erectile** dysfunction.

L2 ANSWER 6 OF 7 PCTFULL COPYRIGHT 2004 Univentio on STN
ACCESSION NUMBER: 2003090747 PCTFULL ED 20031117 EW 200345
TITLE (ENGLISH): TOPICAL TREATMENT OF ERECTILE DYSFUNCTION
TITLE (FRENCH): TRAITEMENT TOPIQUE DE DYSFONCTIONNEMENT ERECTILE
INVENTOR(S): **MILLS, Thomas, M., 760 Oberlin Road, Augusta, GA 30909, US [US, US];**
WINGARD, Christopher, J., 2298 Overton Road, Augusta, GA 30904, US [US, US];
WEBB, R., Clinton, 3832 Honors Way, Martinez, GA 30907, US [US, US];
LEWIS, Ronald, W., 7 Eagleton Court, Augusta, GA 30909, US [US, US];
CHITALEY, Kanchan, A., 2703 Boylston Avenue E, #304, Seattle, WA 98102, US [US, US]
PATENT ASSIGNEE(S): MEDICAL COLLEGE OF GEORGIA RESEARCH INSTITUTE, INC., 1120 15th Street, Augusta, GA 30912-4810, US [US, US], for all designates States except US;
MILLS, Thomas, M., 760 Oberlin Road, Augusta, GA 30909, US [US, US], for US only;
WINGARD, Christopher, J., 2298 Overton Road, Augusta, GA 30904, US [US, US], for US only;
WEBB, R., Clinton, 3832 Honors Way, Martinez, GA 30907, US [US, US], for US only;
LEWIS, Ronald, W., 7 Eagleton Court, Augusta, GA 30909, US [US, US], for US only;
CHITALEY, Kanchan, A., 2703 Boylston Avenue E, #304, Seattle, WA 98102, US [US, US], for US only
AGENT: ROTHSCHILD, Cynthia, B.$, Kilpatrick Stockton LLP, 1001 West Fourth Street, Winston-Salem, NC 27101$, US
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2003090747	A1	20031106

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
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RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2003-US13084 A 20030425
PRIORITY INFO.: US 2002-60/375,872 20020426

L2 ANSWER 7 OF 7 USPATFULL on STN
ACCESSION NUMBER: 2002:243641 USPATFULL
TITLE: Treatment of erectile dysfunction
INVENTOR(S): **Mills, Thomas M.**, Augusta, GA, UNITED STATES
Wingard, Christopher J., Augusta, GA, UNITED STATES
Webb, R. Clinton, Matinez, GA, UNITED STATES
Lewis, Ronald W., Augusta, GA, UNITED STATES
Chitaley, Kanchan, Augusta, GA, UNITED STATES

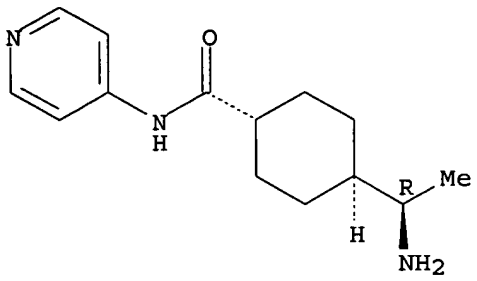
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002132832	A1	20020919	
APPLICATION INFO.:	US 2002-40010	A1	20020104	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-260062P	20010105 (60)
	US 2001-267296P	20010208 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Cynthia B. Rothschild, Esq., Kilpatrick Stockton LLP, 1001 W. 4th Street, Winston-Salem, NC, 27101	
NUMBER OF CLAIMS:	50	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	20 Drawing Page(s)	
LINE COUNT:	1386	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN **331752-47-7** REGISTRY
CN Cyclohexanecarboxamide, 4-[(1R)-1-aminoethyl]-N-4-pyridinyl-, dihydrochloride, monohydrate, trans- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C14 H21 N3 O . 2 Cl H . H2 O
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
CRN (146986-50-7)

Absolute stereochemistry. Rotation (+).



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4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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L7            4 L5

=> d ibib 1-4

L7   ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         2003:892612  CAPLUS
DOCUMENT NUMBER:          139:358813
TITLE:                    Methods using Rho-associated kinase (ROCK) pathway
                          polypeptide modulators for modulating bladder smooth
                          muscle contractility
INVENTOR(S):              Chen, Zunxuan; Hu, Erding; Westfall, Timothy D.;
                          Wibberley, Alexandria
PATENT ASSIGNEE(S):       Smithkline Beecham Corporation, USA
SOURCE:                   PCT Int. Appl., 54 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
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     WO 2003092687      A1   20031113       WO 2003-US13385  20030430
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             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
             PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT,
             TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ,
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             NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
             ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                    US 2002-377504P  P  20020502
REFERENCE COUNT:          2     THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7   ANSWER 2 OF 4  CAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         2003:875110  CAPLUS
DOCUMENT NUMBER:          139:345963
TITLE:                    Rho kinase inhibitors and other agents for the topical
                          treatment of sexual dysfunction
INVENTOR(S):              Mills, Thomas M.; Wingard, Christopher J.; Webb, R.
                          Clinton; Lewis, Ronald W.; Chitaley, Kanchan A.
PATENT ASSIGNEE(S):       Medical College of Georgia Research Institute, Inc.,
                          USA
SOURCE:                   PCT Int. Appl., 53 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
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     WO 2003090747      A1   20031106       WO 2003-US13084  20030425
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MD, RU, TJ, TM
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PRIORITY APPLN. INFO.: US 2002-375872P P 20020426
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:521470 CAPLUS
DOCUMENT NUMBER: 137:73261
TITLE: A RhoA/Rho kinase inhibitor for treatment of erectile dysfunction
INVENTOR(S): Mills, Thomas; Wingard, Christopher; Webb, R. Clinton; Lewis, Ronald; Chitaley, Kanchan
PATENT ASSIGNEE(S): The Medical College of Georgia Research Institute, Inc., USA
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002053143	A2	20020711	WO 2002-US6	20020104

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
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US 2002132832	A1	20020919	US 2002-40010	20020104

PRIORITY APPLN. INFO.: US 2001-260062P P 20010105
US 2001-267296P P 20010208

L7 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:247209 CAPLUS
DOCUMENT NUMBER: 134:271269
TITLE: Analgesics having Rho kinase inhibitory activities
INVENTOR(S): Ueda, Hiroshi
PATENT ASSIGNEE(S): Welfide Corporation, Japan
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001022997	A1	20010405	WO 2000-JP6809	20000929

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            CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                  JP 1999-275854   A  19990929
OTHER SOURCE(S):          MARPAT 134:271269
REFERENCE COUNT:          14    THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


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                            9 JAN 2004      <20040109/UPLS>
MOST RECENT INPADOC WEEK:      200402         <200402/EW>
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     SIMULTANEOUS LEFT AND RIGHT TRUNCATION (SLART) <<<

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                            (LAST UPDATED SEP 9, 2003)  <<<

=> s  WO2001022997/pn
L8            1 WO2001022997/PN
                (WO2001022997/PN)

=> d fam l8

L8    ANSWER 1 OF 1  INPADOC  COPYRIGHT 2004 EPO on STN

PATENT FAMILY INFORMATION
 AN   148185399 INPADOC

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 JP 1999-275854       A  19990929      AU 2000-74512        A  20000929
                                       WO 2000-JP6809       A  20000929
 WO 2000-JP6809       W  20000929      AU 2000-74512        A  20000929

 +--------------AI--------------+      +--------------PI--------------+
 AU 2000-74512        A  20000929      AU 2000074512        A5 20010430
 WO 2000-JP6809       A  20000929      WO 2001022997        A1 20010405

 2 priorities, 2 applications, 2 publications
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L15 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:307008 CAPLUS
DOCUMENT NUMBER: 131:97265
TITLE: Agonist-induced regulation of myosin phosphatase activity in human platelets through activation of Rho-Kinase
AUTHOR(S): Suzuki, Yoshinori; Yamamoto, Masatoshi; Wada, Hideo; Ito, Masaaki; Nakano, Takeshi; Sasaki, Yasuharu; Narumiya, Shuh; Shiku, Hiroshi; Nishikawa, Masakatsu
CORPORATE SOURCE: 2nd and the 1st Departments of Internal Medicine, Mie University School of Medicine, Mie, 514-8507, Japan
SOURCE: Blood (1999), 93(10), 3408-3417
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Human platelets contained about 15 times lower amts. of Rho-kinase than Ca2+/calmodulin-dependent myosin light chain (MLC) kinase. Anti-myosin-binding subunit (MBS) antibody coimmunopptd. Rho-kinase of human platelets, and addn. of GTP.gamma.S-**RhoA** stimulated phosphorylation of the 130-kD MBS of myosin phosphatase and consequently inactivated myosin phosphatase. Two kinds of selective Rho-kinase inhibitors, HA1077 and Y-27632, reduced both GTP.gamma.S-**RhoA** -dependent MBS phosphorylation and inactivation of the phosphatase activity. Activation of human platelets with thrombin, a stable thromboxane A2 analog STA2, epinephrine, and serotonin resulted in an increase in MBS phosphorylation, and the agonist-induced MBS phosphorylation was prevented by pretreatment with the resp. receptor antagonist. HA1077 and Y-27632 inhibited MBS phosphorylation in platelets stimulated with these agonists. These compds. also blocked agonist-induced inactivation of myosin phosphatase in intact platelets. In addn., HA1077 and Y-27632 inhibited 20-kD MLC phosphorylation at Ser19 and ATP secretion of platelets stimulated with STA2, thrombin (0.05 U/mL), and simultaneous addn. of serotonin and epinephrine, whereas these compds. did not affect MLC phosphorylation or ATP secretion when platelets were stimulated with more than 0.1 U/mL thrombin. Thus, activation of Rho-kinase and the resultant phosphorylation of MBS is likely to be the common pathway for platelet activation induced by various agonists. These results also suggest that Rho-kinase-mediated MLC phosphorylation contributes to a greater extent to the platelet secretion induced by relatively weak agonists.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Human platelets contained about 15 times lower amts. of Rho-kinase than Ca2+/calmodulin-dependent myosin light chain (MLC) kinase. Anti-myosin-binding subunit (MBS) antibody coimmunopptd. Rho-kinase of human platelets, and addn. of GTP.gamma.S-**RhoA** stimulated phosphorylation of the 130-kD MBS of myosin phosphatase and consequently inactivated myosin phosphatase. Two kinds of selective Rho-kinase inhibitors, HA1077 and Y-27632, reduced both GTP.gamma.S-**RhoA** -dependent MBS phosphorylation and inactivation of the phosphatase activity. Activation of human platelets with thrombin, a stable thromboxane A2 analog STA2, epinephrine, and serotonin resulted in an increase in MBS phosphorylation, and the agonist-induced MBS phosphorylation was prevented by pretreatment with the resp. receptor antagonist. HA1077 and Y-27632 inhibited MBS phosphorylation in platelets stimulated with these agonists. These compds. also blocked agonist-induced inactivation of myosin phosphatase in intact platelets. In addn., HA1077 and Y-27632 inhibited 20-kD MLC phosphorylation at Ser19 and ATP secretion of platelets stimulated with STA2, thrombin (0.05 U/mL), and simultaneous addn. of serotonin and epinephrine, whereas these compds. did not affect MLC phosphorylation or ATP secretion when platelets were stimulated with more than 0.1 U/mL thrombin. Thus, activation of Rho-kinase and the resultant phosphorylation of MBS is likely to be the

common pathway for platelet activation induced by various agonists. These results also suggest that Rho-kinase-mediated MLC phosphorylation contributes to a greater extent to the platelet secretion induced by relatively weak agonists.

IT 103745-39-7, HA1077 **146986-50-7**, Y 27632
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effects of Rho-kinase inhibitors on phosphorylation of myosin-binding subunit of myosin phosphatase)

L6 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:354307 CAPLUS
DOCUMENT NUMBER: 129:62692
TITLE: Effects of angiotensin converting enzyme inhibition on endothelium-dependent vasodilatation in essential hypertensive patients
AUTHOR(S): Taddei, Stefano; Virdis, Agostino; Ghiadoni, Lorenzo; Mattei, Paola; Salvetti, Antonio
CORPORATE SOURCE: I Clinica Medica, University of Pisa, Pisa, Italy
SOURCE: Journal of Hypertension (1998), 16(4), 447-456
CODEN: JOHYD3; ISSN: 0263-6352
PUBLISHER: Lippincott-Raven Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Essential hypertension is characterized by an impairment of endothelium-dependent vasodilatation. The objective of this study was to test whether antihypertensive treatment with the angiotensin converting enzyme inhibitor lisinopril can improve vasodilatation in response to endothelium-dependent agonists in essential hypertensive patients. We studied the effect of acute (6-8 h after dosing), prolonged (1 mo) and chronic (12 mo) lisinopril treatment on forearm blood flow response (strain-gauge plethysmog.) induced in 10 hypertensive patients (aged 43.6.+-.8.1 yr, blood pressure 151.4.+-.6.8/99.8.+-.3.3 mmHg) by intrabrachial infusions of 0.15, 0.45, 1.5, 4.5, and 15 .mu.g/100 mL per min acetylcholine and 5, 15, and 50 ng/100 mL per min bradykinin, two endothelium-dependent vasodilators, and 1, 2, and 4 .mu.g/100 mL per min sodium nitroprusside, an endothelium-independent vasodilator. At baseline, vascular response was compared with that of 10 normotensive subjects (aged 42.4.+-.6.6 yr, blood pressure 118.4.+-.6.1/77.8.+-.3.4 mmHg). Hypertensive patients had blunted (.**rho**. < 0.01 or less) vasodilatations in response to infusions of acetylcholine (from 3.7.+-.0.3 to 18.3.+-.4.9 mL/100 mL per min) and bradykinin (from 3.7.+-.0.4 to 15.8.+-.2.6 mL/100 mL per min) compared with those of controls (from 3.6.+-.0.3 to 25.3.+-.5.2 mL/100 mL per min for acetylcholine and from 3.7.+-.0.3 to 26.9.+-.4.9 mL/100 mL per min for bradykinin) whereas the responses to infusion of **sodium nitroprusside** were similar (from 3.6.+-.0.3 to 18.5.+-.3.9 and from 3.6.+-.0.3 to 16.4.+-.1.8 mL/100 mL per min, resp.). Acute and prolonged lisinopril treatments significantly (.**rho**. < 0.05 or less) improved vasodilatation in response to infusion of bradykinin (from 3.7.+-.0.4 to 24.5.+-.4.9 and from 3.7.+-.0.3 to 22.1.+-.4.9 mL/100 mL per min, resp.), but not in response to infusions of acetylcholine and of **sodium nitroprusside**. Chronic lisinopril treatment increased (.**rho**. < 0.05) the response to infusions of not only bradykinin (from 3.5.+-.0.5 to 27.6.+-.5.3 mL/100 mL per min), but also of acetylcholine (from 3.5.+-.0.5 to 27.8.+-.8.0 mL/100 mL per min) and **sodium nitroprusside** (from 3.4.+-.0.6 to 25.9.+-.8.5 mL/100 mL per min). However, when the responses to infusions of acetylcholine and bradykinin were normalized with respect to that to infusion of sodium nitroprusside, only the vasodilatation in response to infusion of bradykinin was shown to have been increased by lisinopril treatment. In conclusion, administration of lisinopril to patients with essential hypertension can selectively increase vasodilatation in response to infusion of bradykinin.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Essential hypertension is characterized by an impairment of endothelium-dependent vasodilatation. The objective of this study was to test whether antihypertensive treatment with the angiotensin converting enzyme inhibitor lisinopril can improve vasodilatation in response to endothelium-dependent agonists in essential hypertensive patients. We studied the effect of acute (6-8 h after dosing), prolonged (1 mo) and chronic (12 mo) lisinopril treatment on forearm blood flow response

(strain-gauge plethysmog.) induced in 10 hypertensive patients (aged 43.6.+-.8.1 yr, blood pressure 151.4.+-.6.8/99.8.+-.3.3 mmHg) by intrabrachial infusions of 0.15, 0.45, 1.5, 4.5, and 15 .mu.g/100 mL per min acetylcholine and 5, 15, and 50 ng/100 mL per min bradykinin, two endothelium-dependent vasodilators, and 1, 2, and 4 .mu.g/100 mL per min sodium nitroprusside, an endothelium-independent vasodilator. At baseline, vascular response was compared with that of 10 normotensive subjects (aged 42.4.+-.6.6 yr, blood pressure 118.4.+-.6.1/77.8.+-.3.4 mmHg). Hypertensive patients had blunted (.**rho**. < 0.01 or less) vasodilatations in response to infusions of acetylcholine (from 3.7.+-.0.3 to 18.3.+-.4.9 mL/100 mL per min) and bradykinin (from 3.7.+-.0.4 to 15.8.+-.2.6 mL/100 mL per min) compared with those of controls (from 3.6.+-.0.3 to 25.3.+-.5.2 mL/100 mL per min for acetylcholine and from 3.7.+-.0.3 to 26.9.+-.4.9 mL/100 mL per min for bradykinin) whereas the responses to infusion of **sodium nitroprusside** were similar (from 3.6.+-.0.3 to 18.5.+-.3.9 and from 3.6.+-.0.3 to 16.4.+-.1.8 mL/100 mL per min, resp.). Acute and prolonged lisinopril treatments significantly (.**rho**. < 0.05 or less) improved vasodilatation in response to infusion of bradykinin (from 3.7.+-.0.4 to 24.5.+-.4.9 and from 3.7.+-.0.3 to 22.1.+-.4.9 mL/100 mL per min, resp.), but not in response to infusions of acetylcholine and of **sodium nitroprusside**. Chronic lisinopril treatment increased (.**rho**. < 0.05) the response to infusions of not only bradykinin (from 3.5.+-.0.5 to 27.6.+-.5.3 mL/100 mL per min), but also of acetylcholine (from 3.5.+-.0.5 to 27.8.+-.8.0 mL/100 mL per min) and **sodium nitroprusside** (from 3.4.+-.0.6 to 25.9.+-.8.5 mL/100 mL per min). However, when the responses to infusions of acetylcholine and bradykinin were normalized with respect to that to infusion of sodium nitroprusside, only the vasodilatation in response to infusion of bradykinin was shown to have been increased by lisinopril treatment. In conclusion, administration of lisinopril to patients with essential hypertension can selectively increase vasodilatation in response to infusion of bradykinin.